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MICHEL MORENCY
MINTZ LEVIN
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,601	STRITTMATTER, STEPHEN M.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication app ars on the cover sh et with the correspond nce address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-13,17 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-13,17 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on *2-13-02* is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-5-02 that is a duplicate of the original submission of 4-1-02 has been entered.

2. The Group and/or Art Unit of U.S. Patent application SN 09/485,601 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1647.

3. The declarations via Dr. Strittmatter and Dr. Mueller first submitted 2-13-02 have been fully considered but are not effective to overcome the rejections of record for the reasons set forth below.

Claim Objections

4. Claim 17 is objected to because of the following informalities: "therefore" and "construct" are misspelled within the claim. Appropriate correction is required.

5. Applicant is advised that should claim 7 be found allowable, claim 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim.

See MPEP § 706.03(k). Both claims specify the method of claim 1 wherein the inhibitor is C. botulinum C3 exoenzyme. It is also noted that claim 29 would appear to be a substantial duplicate of claim 28 as both claims appear to be reciting C. botulinum C3 exoenzyme administration. Similarly, claim 29 does not further limit claim 28 but recites the same limitation. Additionally, claim 13 is an apparent duplicate of claim 24.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claim 12 was amended in the response of 4-23-01 to recite the administration of a pharmaceutical composition comprised of mixtures of rho and rac proteins. However, support for the recitation is not noted in the specification as originally filed.

8. Claims 1-2, 6-13, 17 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro stimulation of axon outgrowth with C. botulinum C3 exoenzyme, does not reasonably provide enablement for in vivo promotion of CNS axon growth with generically recited rho protein inhibitors as claimed. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The previous enablement rejection of 8-13-01 is noted and is maintained herein as previously set forth. However, the rejection is reiterated as a scope of enablement rejection to highlight the issues. The issues are whether or not the specification enables the broad scope of the claims. It was previously noted and is reiterated that the specification is enabling for the in vitro promotion of CNS axon outgrowth (via DRG neurons) using C. botulinum C3 exoenzyme. However, it is not agreed that Applicant's specification is enabling to the claimed methods with respect to the in vivo promotion of CNS axon outgrowth in a patient with either C. botulinum C3 exoenzyme or the broad scope of the claims as directed to any rho protein inhibitor, rac protein inhibitor or mixtures for such use.

The previous rejection is further reiterated with respect to the specification's lack of working embodiments in an art accepted model of in vivo CNS axonal outgrowth and the unpredictability associated with extrapolation of in vitro findings to the in vivo CNS situation. Bartsch et al., previously of record is noted with respect to teaching the necessity to test and confirm in vitro findings in vivo with respect to the CNS. Lehman et al., previously of record is noted with respect to post-filing date evidence (9-1-99) of C3 exoenzyme induced optic nerve outgrowth (regeneration) following optic nerve crush.

The specification at pp. 16, lines 12-16 notes that C. botulinum C3 exoenzyme was the only protein altering rho activity that altered dorsal root ganglia outgrowth in

culture. The treated neurites were observed to double their outgrowth or extension following treatment. Page 18, lines 3-13 note the specificity of C3 action in inhibition of rho activity through ADP-ribosylation and pp. 23, line 20-pp. 24, line 3 teach a C3 expressing adenovirus vector that was able to infect neurons both in vitro and in vivo as measured by EGFP expression. While it was noted that the C3 virus infected in vitro cultures were rendered insensitive to semD and myelin, the specification is silent as to any effect in promoting CNS axon outgrowth either in vitro or in vivo using the adenovirus C3 construct. Thus, there is no exemplification or enablement for a method for promoting CNS axon growth in a patient (in vivo) as claimed. Moreover, C. botulinum C3 exoenzyme is the only rho inhibitor noted that effects axonal growth by promoting neurite extension and the finding is only exemplified in vitro.

Applicants argue in the response of 2-13-02 that a declaration by Dr. Strittmatter presented the same date points out that, "investigators in the field routinely employ in vitro models in the initial phases of neuronal research, as these are often predictive of in vivo results and are more convenient and economical than in vivo experiments at the outset of research on a given system. The properties of rho proteins and their inhibitors have not been observed to be different in vitro and in vivo in literature reports, and the results of Applicant's in vitro experiments have been confirmed in vivo." Applicants further argue with respect to the Bartsch reference that the reference evidences that typical research protocols involve in vitro experiments followed by in vivo work. Applicants argue that if in vitro work was not predictive of in vivo results, scientists would not bother to use in vitro work. Applicants further note that Bartsch's

findings are not corroborated by others that report MAG inhibits axon outgrowth in vitro and in vivo, see in particular Lehman et al., J. Neurosci., 19:7537-47, 1999.

The Strittmatter declaration notes another rho inhibitor Y-27632 that exhibits in vitro and in vivo axon regeneration. However, the Takemoto reference to which Applicant refers is a post-filing date publication and the particular teachings contained therein were not apparently known or disclosed by Applicants in instant application.

Applicants further point to a declaration and experiments conducted via Bernhard Mueller. These experiments confirm neurite outgrowth promoting effects of in vivo with C2/C3 exoenzyme in a spinal cord lesion model. However, the specification as filed failed to disclose Dr. Mueller's specific teachings, and the declaration fails to disclose dates his experimentation were completed or were first publicly disclosed. While such is not required such information is relevant to the timeline of Applicants invention with respect to enablement. It is noted that a similar construct to the Mueller work was published by Barth et al., Infection and Immunity, 66(4):1364-1369, April 1998. Thus, while the declaration notes enablement of particular embodiments within the scope of the invention, the declaration does not address the full scope of the claims or speak to the predictability of extrapolating in vitro data to in vivo findings. Further the experimentation completed by Mueller was neither disclosed in instant application nor apparently known by the artisan at the time of the invention by Applicants.

Applicant's further note the post-filing date publication via McKerracher et al., and argue that the claim limitations directed to mechanical introduction, effects in spinal cord injury, white matter stroke, and traumatic brain injury support enablement by

Applicant's. Applicants argue that a number of rho inhibitors are known but reference only post-filing date publications and/or declarations.

Applicant's arguments filed 2-13-02 have been fully considered but are not persuasive. While Applicants arguments and declarations attest to the enablement of particular embodiments within the scope of Applicant's claims, the arguments and evidence are not persuasive to show that applicant's specification was enabling for the full scope of the invention as claimed, at the time of filing. The information cannot establish enablement of the invention as disclosed by the specification. The effects of alternative rho-inhibitors is not disclosed in the specification. Further, the effect of CNS axon growth in patients in vivo is not disclosed or exemplified.

As previously noted, the art evidences the unpredictability in extrapolation of data from in vitro experiments. Applicants arguments submitted 2-13-02 at pp. 1-2 also appears to recognize that the art expects and/or requires that in vitro findings be confirmed via in vivo experimentation, particularly in unpredictable arts such as in in vivo experimentation of the CNS. Further with regard to the specifics of an "effective amount", the particulars of administration and the required effects of promoting axon outgrowth in patients with spinal cord injury, white matter stroke or traumatic brain injury, the specification is required to enable the artisan to practice the invention without further undue experimentation. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex

parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

The claims are drawn to a method of promoting CNS axon growth in a patient of axon regeneration by administering an effective amount of at least one rho protein inhibitor whereby neurite outgrowth is stimulated. To practice such a method would require a knowledge of the route, duration and quantity of administration of that rho inhibitor to a subject and this information is not provided by the instant specification. The text clearly fails to supply the guidance that would be needed by a routine practitioner because no in vivo exemplification of such method is provided. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method was practiced in the art with a different agent or to provide even a single working example, prophetic or actual, of the claimed method. In the absence of this guidance a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of the rho protein inhibitor of the instant invention and in determining a suitable route of administration. It is further noted that the only inhibitor disclosed as having such activity in the specification is C. botulinum C3 exoenzyme. The instant situation is directly analogous to that which was addressed in *In re Colianni*, 195 U.S.P.Q. 150,(CCPA 1977), which held that a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequence, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not

meet requirements of 35 U.S.C. 112 first paragraph".

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot following the guidance presented therein, practice the claimed method without first making a substantial inventive contribution. The artisan would be required to determine how to effect promotion of central nervous axon outgrowth in a patient in need thereof by administration of a rho protein inhibitor such that outgrowth is stimulated. There is no guidance on this matter within the specification as originally set forth. The artisan must choose the inhibitor, the particular patient, the amount of selected compound, a suitable delivery method, dosage regime and duration for adequate response. These selections would only after further undue experimentation arrive at the invention now claimed.

Thus, Applicants arguments and declarations of Dr. Strittmatter and Dr. Meuller fail to evidence enablement of the invention as filed.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2, 6-13, 17 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained as set forth in the previous action of 8-13-01 although it is noted that particular (dependent) claims appear to have been inadvertently omitted from the rejection. Applicants now argue that the recitation is definite in light of the guidance at p. 12 and in the literature. Applicants also note arguments presented in a 1.132 declaration via Dr. Strittmatter.

Applicant's arguments and declaration have been fully considered but are not persuasive for the following reasoning. The guidance at p. 12 of the specification is general in nature and does not delimit a particular assay for the determination of rho inhibition. In addition, the Strittmatter declaration references no less than 6 different assays to determine rho inhibition including measurements of actin cytoskeleton dynamics, transcriptional regulation, cell cycle progression, programmed cell death, transformation and membrane trafficking. The declaration and arguments also reference multiple literature as to measurements of different proteins, activities and assays that should be considered as suitable. However, none of these alternative choices provides a definitive means for assessing whether or not a compound should or should not be considered a rho inhibitor. Further there is no clarification of the subgenus of rho inhibitors that may inhibit rac or of constructs having ADP-ribosylation

activity deleted thereferom and C3 activity substituted therefore. Because there is no standard assessment of rho inhibition or rac inhibition that is recognized within the art and because the specification fails to teach which of the multitude of choices should be used, the metes and bounds of the claims cannot be determined.

11. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 is indefinite because the recitation is a clause that lacks reference to the preceeding method. It appears that it is applicant's intention to further recite the method according to claim 12 wherein, "the rho protein inhibitor comprises C. botulinum C3 exoenzyme." Clarification is required.

12. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 recites "the C. botulinum C3 inhibitor" where no antecedent basis for the recitation is noted within claim 28. It is also noted that claim 29 would appear to be a substantial duplicate of claim 28 as both claims appear to be reciting C. botulinum C3 exoenzyme administration.

13. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 recites "the composition" where no antecedent basis for the recitation is noted within claim 28. It is also noted that the claim recitation would appear to be more properly written as a dependent claim since the recitation does not appear to further limit the enzyme, but alternatively recites the administration

of a chimeric construct that differs in structure and function from C3 exoenzyme. Alternatively the recitation must be rewritten as clearly dependent from C. botulinum C3 exoenzyme, i.e., "wherein the C. botulinum C3 exoenzyme is a chimeric construct having....".

14. Claims 8, 17 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims use alternate terminology with respect to "C3 exoenzyme" and "C3 enzyme". Applicant's should use the same terminology or specify the difference in the enzymes (and their activities) that are alternatively recited.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

As previously noted the effective filing date of claims 8 and 17 drawn to a C2/C3 exonenzyme construct having the actin ADP-ribosylation activity deleted from the C2 toxin and the C3 enzyme activity substituted therefore, so that the construct ADP-

ribosylates rho specifically and inactivates the G protein is 8-12-1998 based on a lack of support in the provisional as originally filed.

Further it is noted that instant claims 1-2, 6-13, 17 and 21-30 are drawn to administration to a patient, patients suffering from acute or chronic spinal cord injury, white matter stroke, traumatic brain injury and administration of rho inhibitors via mechanical introduction to the axons or their non-neuronal support tissue. While the priority application appears to contemplate in vitro administration for effecting CNS axon outgrowth, the Examiner cannot find support in the provisional for the recitations as noted above directed to administration to a patient, to patients suffering from acute or chronic spinal cord injury, white matter stroke, traumatic brain injury or to patients via mechanical introduction to the axons or their non-neuronal support tissue. All experimentation is directed to the in vitro model system and no recitation of administration to a patient is found. Moroever, the provisional appears similarly limited to the effects of axon growth based soley on the rho inhibitor C3 exoenzyme Clarification of support for the scope of the claims is required for benefit of the 8-13-1997 date. Thus, the effective filing date of claims 1-2, 6-13, 17 and 21-30 is the filing date of 8-12-1998.

Claim Rejections - 35 USC § 102 or 103

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 2, 6, 12, 21-22 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartsch et al., Neuron, 15:1375-81, 1995 or in the alternative under 35 U.S.C. 103(a) as obvious over Bartsch et al., Neuron, 15:1375-81, 1995.

Bartsch et al teach increased axonal regrowth following optic nerve crush in wild-type and MAG-deficient mice after application of the IN-1 antibody directed against the neurite growth inhibitors NI-35 and NI-250. Thus, the reference teaches the limitations of the claims with the exception that the reference is silent as to whether or not the IN-1 antibody is a compound/composition that is a rho/rac protein inhibitor. The application is silent as to how rho/rac inhibition such should be assessed. However, the Strittmatter declaration references no less than 6 different assays to determine rho inhibition including measurements of actin cytoskeleton dynamics, transcriptional regulation, cell cycle progression, programmed cell death, transformation and membrane trafficking. IN-1 is noted to exhibit neurite growth, a form of actin cytoskeleton dynamics and membrane trafficking and thus the IN-1 antibody would appear to be a rho/rac inhibitor via it's acitivities. The USPTO has insufficient resources to determine whether or not the IN-1 antibody is a compound that in fact exhibits rho/rac protein inhibition. Thus, the Examiner has insufficient facts to determine whether the Bartsch treatment is "inherently

the same" or obvious since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that the IN-1 antibody is or is not a rho/rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

18. Claims 1, 2, 6, 12, 21-22, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Sylvain et al., Pediatric Neurology, 10(3):228-32, 1994 as evidenced via Eberlein et al., Br. J. Pharmacol., 133:1172-1180, 2001.

Lovastatin is a recognized rho inhibitor as evidenced via Eberlein et al., Br. J. Pharmacol., 133:1172-1180, 2001 as referenced within the Strittmatter declaration. Sylvain et al., teach magnetic resonance spectroscopy in Niemann-Pick disease type C: correlation with diagnosis and clinical response to cholestyramine and lovastatin. As disclosed in the abstract, "Niemann-Pick type C is an autosomal-recessive, neurovisceral storage disorder that results from defective cholesterol esterification. Cholesterol-lowering agents have been demonstrated to decrease hepatic lipids in Niemann-Pick type C patients. The objective was to determine the effects of cholesterol-lowering agents on neurologic features and to develop a noninvasive method of monitoring clinical response. A 9-month-old boy with progressive hepatosplenomegaly and neurodevelopmental delay was studied. Water-suppressed proton magnetic resonance spectra from a supraventricular volume of central white and gray matter revealed an abnormal lipid signal. The patient was treated with

cholesterol-lowering agents (i.e., cholestyramine, lovastatin). Repeat standardized neurodevelopmental assessments (Peabody and Griffith scales) at 13 and 19 months were normal and magnetic resonance spectra no longer detected the previously observed lipid resonance. Early treatment of Niemann-Pick type C patients with cholesterol-lowering agents appeared to have short-term beneficial effects. Magnetic resonance spectra provided a noninvasive means of monitoring CNS response."

Thus Niemann Pick is a neurodegenerative disease in a patient and the treatment comprises the administration of a rho inhibitor in the quantity of 0.125 mg/kg daily, gradually increased to 1.0 mg/kg b.i.d. after 8 weeks as set forth in methods, p. 229, column 2, lines 10-16. While the reference is silent as to whether or not this quantity is sufficient to stimulate neurite outgrowth it is noted that the treatment produced a beneficial response in CNS pathology as assessed via magnetic resonance spectra. Thus, the Sylvain treatment is deemed effective to block the degenerative effects of the disease and to promote neurite outgrowth. Therefore the treatment is deemed anticipatory absent convincing factual evidence to the contrary. The Nieman-Pick patient is a patient in need of axon regeneration as a result of the storage disorder. The delivery is via injection and is thus by means of mechanical introduction. Dissemination in the body via the bloodstream would effectively deliver the inhibitor to the axons or their non-neuronal support tissue.

The reference is silent as to whether or not the inhibitor is one that inhibits rac in addition to rho. Thus, the USPTO has insufficient resources to determine whether or not the lovastatin administration is sufficient to inhibit a rac protein. Thus, the Examiner

has insufficient facts to determine whether the Sylvain treatment is "inherently the same" or obvious as claimed in claim 6, since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that the lovastatin administration of Sylvain is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

19. Claims 1, 2, 6, 9, 11-12, 21-22 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Varon et al., J. of Neurotrauma 11(5):473-486, 1994 as evidenced by Takahashi et al., Biochem. & Biophys. Res. Communications, 190(3):1156-62, 1993.

Varon et al., teach two models a septo-hippocampal lesion model representing traumatic brain injury and a spinal cord sensory regeneration model representing spinal cord injury. In both models nerve growth factor administration mediates CNS axon regeneration and neurite outgrowth effects in the animal patients. However, the Varon reference is silent as to the rho/rac inhibiting properties of NGF. Takahashi et al., teaches that NGF at 50 ng/ml is effective to inhibit the ADP-robosylation of the rho protein via an indirect mechanism, see in particular abstract and results. The Takahashi reference evidences that ngf exhibits rho inhibiton and thus the molecule qualifies as a rho inhibitor. However, the references are silent as to whether or not NGF exhibits rac inhibition in addition to the rho inhibition. The USPTO has insufficient resources to determine whether or not NGF is sufficient to inhibit a rac protein. Thus, the Examiner has insufficient facts to determine whether the treatments are "inherently the same" or

obvious as claimed, since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that NGF is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

20. Claims 1-2, 6-7, 12-13, 21-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al., US Patent 5,851,786 filed September 27, 1995 and issued Dec. 22, 1998.

Johnson et al., teach, "methods useful for identifying compounds capable of specifically regulating actin polymerization, stress fiber formation or focal adhesion assembly by regulating G.sub..alpha.12 and/or G.sub..alpha.13 activity in cells involved in inflammatory responses, immune responses, allergic responses and neuronal responses, kits to perform such assays and methods to control disease related to such responses," see in particular Abstract. Johnson et al., teach Example 3, regulation of Rho protein activity by G.sub..alpha.12 QL and G.sub..alpha.13 QL that is Rho-dependent. In particular Johnson discloses that Botulinum C3 Exoenzyme is an effective reagent for stimulating Rho-dependent stress fiber formation and focal adhesion assembly, see in particular Example 3A and 3B. Johnson concludes,"that G.alpha..sub.12 and G.alpha..sub.13 regulate Rho dependent actin polymerization resulting in stress fiber formation and the assembly of focal adhesions. Thus, the results clearly demonstrate that alpha..sub.12 and .alpha..sub.13 integrate heterotrimeric G protein-coupled receptors with the regulation of Rho. The results further indicate that

G.sub..alpha.12 and G.sub..alpha.13 have similar ability to stimulate Rho-dependent stress fiber formation and focal adhesion assembly. Thus, G.sub..alpha.12 and G.sub..alpha.13 can interact with a common regulator regulating Rho activation," see in particular abstract, Example 3 and columns 17-18.

Johnson et al., further teaches that such molecules are useful as therapeutic compositions for preventing and treating diseases involving abnormal growth or migration of cells and are particularly useful for preventing or treating diseases involving a neuronal response. Further Johnson teaches prevention or treatment of the neurodegenerative diseases Parkinson's disease and Alzheimer's disease, see in particular Detailed Description, paragraph 60 and claim 40. Thus, while the reference is silent as to the recitations of "promoting neurite outgrowth" and "a patient in need thereof" the reference anticipates the claimed invention because the reference teaches administration of the preferred compounds to individuals with a neurodegenerative disease, namely Alzheimer's and Parkinson's which patients are indeed "in need of axon regeneration" or "neurite outgrowth" as claimed. Johnson notes his treatment is effective and thus the amounts are deemed to provide neurite outgrowth absent convincing factual evidence to the contrary. The administraion includes via mechanical administration such as with an osmotic pump and comprises a suitable carrier, see in particular column 15.

The Johnson et al., reference is silent as to whether or not the C3 exoenzyme inhibits rac in addition to inhibiting rho. However, it is noted that C3 exoenzyme is the only molecule noted by applicants to exhibit neurite outgrowth. While the specification

also does not specifiy that C3 exoenzyme inhibits rac, such is presumed by the Examiner based upon Applicant's claim structure. Evidence to the contrary would support the enablement rejection of record with respect to a lack of enablement to the breadth of molecules encompassed by the claims. Moreover, such would appear to evidence a total lack of enablement for any such rac inhibitor as claimed. The USPTO has insufficient resources to determine whether or not the C3 exoenzyme a compound that exhibits rac protein inhibition. Thus, the Examiner has insufficient facts to determine whether the Johnson treatment is "inherently the same" or obvious since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that the C3 exoenzyme is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

21. Claims 1, 2, 6, 10, 12, 21-22 and 25-27 are rejected under 35 U.S.C. 103(a) as being obvious over Mattson et al., Stroke 1993, 24(12):I136-40; discussion I144-5, Olson et al., J. of Neurol., 1994 Dec., 242 (1Suppl. 1):S12-15 and Olson et al., Acta Neurochirurgica Supplementum, 1993, 58(3-7), Varon et al., J. of Neurotrauma 11(5):473-486, 1994 and as evidenced by Takahashi et al., Biochem. & Biophys. Res. Communications, 190(3):1156-62, 1993.

Mattson et al., teach protection of CNS neurons in culture from neuronal damage and death in a stroke model via treatment with nerve growth factor.

Mattson et al., do not teach such protection in a patient.

Olson et al., 1993 and Olson et al., 1994 teach the similarity in protection via nerve growth factor administration amongst different CNS model systems and predict its general applicability not only in the neurodegenerative diseases but for treatment of ischemia, stroke and injury, see in particular abstract.

Varon et al., further evidences the wide use and acceptance of NGF treatment in a variety of CNS diseases, specifically for the promotion of neuronal cell survival, growth and regeneration both in vitro and in vivo.

Thus, the skilled artisan would be motivated as suggested by Olson et al., 1993 and Olson et al., 1994 to treat stroke and ischemia injuries with nerve growth factor to provide for neuronal survival, neurite outgrowth and regeneration within the CNS. One of skill in the art would have expected success in such treatment based upon the success of NGF in the treatment of CNS injuries in other model systems as evidenced by Varon and the teachings of Mattson et al., that NGF is protective to CNS neurons in a culture model of CNS stroke ischemia. Thus the cumulative reference teachings render the claims obvious to the artisan.

As set forth above with respect to rac inhibition, Takahashi et al., teaches that NGF at 50 ng/ml is effective to inhibit the ADP-robosylation of the rho protein via an indirect mechanism, see in particular abstract and results. The Takahashi reference evidences that ngf exhibits rho inhibiton and thus the molecule qualifies as a rho

inhibitor. However, the references are silent as to whether or not NGF exhibits rac inhibition in addition to the rho inhibition. The USPTO has insufficient resources to determine whether or not NGF is sufficient to inhibit a rac protein. Thus, the Examiner has insufficient facts to determine whether the treatments are "inherently the same" or obvious as claimed, since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that NGF is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

22. Claims 1-2, 6-13, 17 and 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamata et al., Microbiol., Immunol., 38(6):421-428, 1994, Varon et al., J. of Neurotrauma 11(5):473-486, 1994, Mobley et al., 5,134,121 July 28, 1992, Mattson et al., Stroke 1993, 24(12):I136-40; discussion I144-5, Olson et al., J. of Neurol., 1994 Dec., 242 (1Suppl. 1):S12-15 and Olson et al., Acta Neurochirurgica Supplementum, 1993, 58(3-7) and Barth et al., Infection an Immunity 66(4):1364-69, April 1998.

Kamata et al., teach chick dorsal root ganglia (DRG) induced nerve outgrowth via administration of C botulinum C3 exoenzyme (ADP-ribosyltransferase) that is at least as effective as DRG outgrowth induced via the neurotropic factor NGF, see in particular abstract, Effects of C3 exoenzyme on the morphology of cultured cells, pp. 424-425 pp. 427, lines 2-23. Based on such evidence Kamata et al., conclude that C3 exoenzyme is

a neurotropic agent. DRG cells contain both central and peripheral projections and thus the outgrowth is of CNS although the outgrowth is in culture.

Kamata et al., fail to teach in vivo administration of C3 exoenzyme to promote neuronal outgrowth within the CNS in a patient.

Varon et al., teach that neurotrophic factors are well recognized for their important function on developing neurons of the PNS, to prevent or reduce degenerative responses of adult CNS to a variety of diseases and injuries, and in the regeneration of adult CNS in animals. Varon et al., further teach various model systems utilizing in vivo administration of NGF to promote neuronal outgrowth in the CNS in vivo. NGF is a molecule that has been isolated as a neurotophic factor based upon it's ability to promote neurite outgrowth in dorsal root ganglia assays.

Mobley et al., similarly teach NGF and NGF variants that are useful in the treatment of multiple neurological diseases via the mechanism of promoting neurite outgrowth, see in particular columns 6-7 and 16-18. Mobley et al., further teach that a suitable assay to screen for such molecules is via assessing the ability of a molecule to promote neuronal outgrowth in cultured dorsal root ganglia cultures, see Bioassay with dorsal root ganglia neurons, columns 19-20.

Mattson et al., teach protection of CNS neurons in culture from neuronal damage and death in a stroke model via treatment with nerve growth factor.

Olson et al., 1993 and Olson et al., 1994 teach the similarity in protection via nerve growth factor administration amongst different CNS model systems and predict its

general applicability not only in the neurodegenerative diseases but for treatment of ischemia, stroke and injury, see in particular abstract.

Barth et al., teach a C2/C3 fusion protein wherein the full-length C3 ADP ribosylransferase of Clostridium limulosum is inserted to the C2IN Nterminal part that enters the cells via the binding component and thus increases the sensitivity of the target cell for C3 activity by at least several hundred fold.

Thus, Mobley et al., and Varon et al., Mattson et al., Olson et al., 1993 and Olson et al., 1994 teach the recognition in the art of neurotrophic factors to promote axon outgrowth in the CNS for a wide variety of diseases via mechanical introduction in patients. Mobley et al., further evidences that a suitable assay for predicting such effects is the dorsal root ganglia assay that was originally used in the characterization of NGF and now a multitude of known neurotrophic factors that are effective both in vitro and in vivo to promote neurite outgrowth within the PNS and the CNS in patients. Thus, one of skill in the art would have been motivated based on Kamata's teachings of C3 exoenzyme as a neurotrophic factor capable of stimulating CNS neuronal outgrowth in dorsal root ganglia cultures to use the same molecule to produces such effects in vivo in a patient in need of CNS axon outgrowth. One of skill in the art would have expected success using such a method based on C3 exoenzyme's activity in promoting CNS axon outgrowth from DRG neurons in vitro and the art's teachings of such assays in predicting utility in promoting neurite outgrowth in the CNS of patients. One of skill in the art would have been further motivated to utilize a C2/C3 fusion construct as taught by Barth et al., that provides for the same effect but with several hundred fold sensitivity

as exemplified via Barth. Thus, the cumulative reference teachings render the invention obvious to the skilled artisan.

These rejections are not in conflict with the enablement rejection above. As stated in Ex parte Dash, 27 UPQ2d 1481 (BdPatApp&Int, 1993("[w]e are not unaware that we are sustaining rejections under lack of enablement based on reasons which also apply to the prior art" and "[I]f appellants overcome the lack of enablement of their claims, tey will necessarily overcome the lack of enablement of the references". All of the elements of the claimed invention were in the prior art. Further, the instant specification provides neither an element of predictability that was lacking from the prior art or the disclosure of unexpected results.

We recognize that In order for a reference to be anticipatory, it must be enabling. See In re Le Grice, 301 F. 2d 929,936, 133 USPQ 365, 371 (CCPA 1962) ("[B]efore any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in posssession of the invention."), In re Donohue, 766 F.2d 531, 533, 226 USPQ 619,621 (Fed. Cir. 1985) (reaffirming La Grice; but In re Hafner, 410F.,2d 1403, 1405, 161 USPQ 783, 785 (CCPA 1969) (finding that a disclosure that fails to teach how to use a disclosed compound, while it may serve as an anticipatory reference under 35 USC 102 may fail to support the claimed invention as required by 35 USC 112, first paragraph; In re Schoenwald, 964 F.2d 1122, 1123-24, 22 USPQ2d 1671, 1673, (Fed. Cir. 1992) (following the reasoning of In re Hafner, In re Lukach, 442 F.2d 967, 970, 169 USPQ 795, 797 (CCPA 1971) (noting that "there

are...apparent anomalies between the requirements for claim-anticipating disclosures and claim-supporting disclosures"). In circumstances such as this, however, where the specification does not appear to add anything not taught by the prior art, the examiner may not have sufficient evidence to determine which rejection is more appropriate, i.e., the art rejection or the enablement rejection. If the specification is enabling, so is the prior art reference, and vice versa.

In this regard, the statements of the Court of Claims and Patent Appeals in In re Krauch, 56 F.2d 290, 12 USPQ 257 (CCPA 1932), are enlightening. In that case, the Commissioner urged, and the CCPA agreed, that Krauch's claims were unpatentable on the basis of alternate theories. The court noted that it did not have to choose between the two alternative theories as the result was the same no matter which theory was accepted-appellants were not entitled to allowance of the appealed claims. See id. at 291-92. The reasoning of Krauch is germane to the situation where the teachings of the specification appear to be commensurate with the disclosure of a previously published reference. If the specification is enabling, so to is the reference, and the claims may be unpatentable over the teachings of that reference. If the reference is not enabling, neither is the specification, and the claims may again be unpatentable. The Examiner need not choose based on the limited evidence the rejection that is the more correct one, as the result is the same in either instance-the claims are unpatentable. It is thus proper for the Examiner to make the superficially inconsistent art and enablement rejections, and place the burden on applicant to distinguish his or her specification from

the prior art and to point out how the specification goes beyond and elaborates upon what is taught by the previously published reference(s).

The instant case appears to fall squarely within the bounds of the above analysis and thus both 35 USC 112, first paragraph and 35 USC 103 rejections are set forth herein. It is noted that Applicants traverse the enablement rejection of record, in part, by noting that "If in vitro experiments were not predictive of in vivo results, scientists wouldn't bother with in vitro work ", see also 37 CFR 1.132 declaration via Dr. Strittmatter, "My finding that rho protein inhibitors such as the C3 exoenzyme used in my application's examples promot central nervous system axon regeneration was first observed in in vitro experiment, which most investigators in the field use in initial experiments because they are predictive of in vivo physiology". Thus, it appears to be Applicant's opinion that the disclosure of the in vitro experimentation in DRG neurons is all that is required to enable the artisan to practice the claimed invention. If this is so then it also appears clear that the invention was both enabled and anticipated via Kamata et al., Microbiol., Immunol., 38(6):421-428, 1994 which teach the same CNS axon outgrowth in DRG neurons in culture via administration of C3 exoenzyme.

While it is noted that the Kamata referenceis silent as to the particulars of CNS administraion to a patient as claimed and via mechanical introduction, it is noted that each of these particulars were already of general knowledge to the artisan in the field. Such is evidenced via the disclosures of Varon, Mattson, Olson et al., 1993 and Olson et al., 1994 including administration via mechanical means, in vivo to patients with various neurological disorders including in spinal cord injury, white matter stroke and

traumatic brain injury. Further the advent or a pharmaceutical composition comprising a carrier or even the particular C2/C3 construct is intrinsic. Motivation to use them are provided by the art's recognition of suitable pharmaceutical formulations to provide increased delivery to and sensitivity of the cells. Thus, it would appear that all remaining differences betweeen the prior art disclosures and Applicant's claims are general skills known to the artisan and would be obvious therefore. Accordingly, the facts are similar to that as noted in Ex parte Dash and In re Krauch above. All of the elements of the claimed invention were in the prior art. Further, the instant specification provides neither an element of predictability that was lacking from the prior art nor the disclosure of unexpected results. If the specification is enabling, so to is the reference, and the claims may be unpatentable over the teachings of that reference. If the reference is not enabling, neither is the specification, and the claims may again be unpatentable.

Status of Claims

23. No claims are allowed.

24. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is

(703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
June 3, 2003

Gary L Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600